REMARKS

This application is a continued prosecution application filed pursuant to 37 C.F.R. §1.53(d). The instant Office Action, at page 2, acknowledges the filing of a Preliminary Amendment (filed *via* facsimile on May 22, 2002) by which new claims 44-59 were added to the application. Therefore, claims 1-14 and 43-59 are pending in the application. For the Examiner's convenience, all of the pending claims are set forth in Appendix A.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or in one or more separate applications.

Rejection of Claims Under 35 U.S.C. §112, First Paragraph

Claims 1-14 and 43-59 are rejected under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for a mutant IL8 receptor and a mutant galanin receptor, does not reasonably provide enablement for any other mutant mammalian G protein coupled receptor." The Office Action, at page 2, indicates that "[t]here is not adequate guidance as to the nature of the mutant mammalian G protein coupled receptor which Applicants claim." The Office Action further indicates that "[t]he specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with this claim." Applicants respectfully traverse this rejection.

Independent Claims 44, 52, and 53 and the Claims Depending Therefrom

It is Applicants' position that at a minimum, independent claims 44, 52 and 53, and the claims depending therefrom, are fully enabled. To begin with, Applicants invite the Examiner's attention to page 2 of the Office Action in which the ***Office Action admits that the specification is "enabling for a mutant IL8 receptor and a mutant galanin receptor."*** Applicants respectfully submit that claims 44-49 were added by way of a Preliminary Amendment filed *via* facsimile on May 22, 2002 upon the indication in the Office Action dated February 26, 2001 that both the mutant IL8 receptor and a mutant galanin receptor were fully enabled.

In particular, Applicants respectfully submit that claim 44, drawn to a mutant mammalian IL8 receptor that (1) contains the motif $X_1X_2X_3X_4$ and (2) contains at least one point mutation in the motif $X_1X_2X_3X_4$ selected from the group consisting of: Arg to Trp at position 73, Met to Ile at position 246 and Gly to Arg at position 320, which gives the receptor greater signaling ability than is observed in the wild type receptor. Applicants teach the specific mutations in the $X_1X_2X_3X_4$ motif in the IL8A receptor which causes increased signaling (See Example 2). Thus, the nature of the invention is clearly taught by Applicants.

Likewise, Applicants respectfully submit that independent claim 52 is drawn to a mutant galanin receptor-1 that (1) contains the motif $X_1X_2X_3X_4$ and (2) contains at least one point mutation in the motif $X_1X_2X_3X_4$ with Gly to Ala at position 320, which gives the receptor greater signaling ability than is observed in the wild-type receptor. In addition, independent claim 53 is drawn to a mutant galanin receiptor-1 that (1) contains $X_1X_2X_3X_4$ motif and (2) comprises a seventh transmembrane domain with a carboxy terminal end, which causes increased signaling as compared to the wild-type receptor (see Example 3). Applicants respectfully submit that claims 52 and 53 are clearly taught in Example 3 of the instant specification. Furthermore, the examples of the present invention teach how to generate, for example, the mutant galanin receptor-1 as well as establishing a correlation between the function of the mutant galanin receptor-1 and specific amino acids within the $X_1X_2X_3X_4$ motif (See Example 3).

Based on the foregoing, it is evident that following the teachings in Applicants' specification and the knowledge generally available in the art at the time of the invention, the skilled artisan would be able to make and use the claimed invention using only routine experimentation. In view of all of the forgoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 44-59 under 35 U.S.C. §112, first paragraph.

Independent Claim 1 and Claims 2-14 and 43 Depending Therefrom

It is Applicants' position that claims 1-14 and 43 satisfy the *Wands* factors, upon which the Examiner is apparently relying in rejecting the claims. Applicants respectfully submit that it would be routine for one of ordinary skill in the art to generate a mutant GPCR containing a mutation in the $X_1X_2X_3X_4$ motif, which causes increased signaling as compared to the wild-type GPCR.

(1) Breadth of the Claims Are Reasonable Given the Teachings of the Instant Specification and Sufficient Guidance and Direction Have Been Presented By The Present Invention

The Office Action sets forth the allegation that "[t]he claims included in the instant rejection recite the functional limitation that the encoded protein can generate a signal greater than the signal generated by a wild-type protein" (see page 4 of the Office Action). The Examiner appears to doubt that the encoded mutant protein can in fact generate a signal greater than the signal generated by a wild-type protein. However, the disclosure of invention set forth by Applicants in their application must be given the presumption of correctness and operativeness by the PTO, and the only relevant concern of the PTO under the circumstances should concern the truth of the assertions contained in the application. *In re Marzocchi*, 439 F.2d 220, 169 U.S.P.Q. 367 (C.C.P.A. 1967); see also, *In re Bowen*, 492 F.2d 859, 181 U.S.P.Q. 48 (C.C.P.A. 1974). The Examiner proffers nothing but conjecture to controvert the truth of Applicants' assertions in the instant application.

Applicants have provided working examples that disclose how to make and express GPCRs of the instant invention, and have specifically shown that the mutant GPCRs do in fact generate a greater signal than that generated by the wild-type receptor. In this regard, the Examiner's attention is invited to Example 2, page 65, line 36 through page 66, line 10. In particular, Example 3 details the generation of a mutant galanin receptor-1 (GalR1) based upon a mutation that was shown to increase IL-8A receptor signaling (page 67, lines 10-48 of the specification). The mutation that increased the IL-8A receptor response to ligand similarly caused an increased response to ligand in the Ga1R1 as well. In short, the working examples of the present invention demonstrate a correlation between the function of GPCRs, *i.e.*, enhanced signaling, and specific amino acids within the $X_1X_2X_3X_4$ motif. Applicants have clearly identified this motif, provided the location of this motif in the protein, and also provided the candidate amino acids for this motif. In addition, Applicants have actually demonstrated increased signaling by the mutant receptor as compared to the wild-type receptor.

(2) Nature of the Invention

The Office Action appears to indicate that because the nature of the invention is a mutant protein, this would somehow cause one of ordinary skill in the art to exercise undue

experimentation in making and using the invention. However, the Office Action does not set forth any explanation as to why this would be so. Applicants assert that the area of mutant proteins was well studied and developed at the time the invention was made, such that much was known to those of ordinary skill in the art about how to make mutations in proteins. In this regard, Applicants have taught much on the subject as is evidenced in the instant application at, for example, page 29, line 33 through page 31, line 21, where applicants give significant guidance on the subject of mutations in G proteins. In addition, working Examples 2 and 3 specifically teach how mutations can be made in IL-8 and human galanin-1 receptors, respectively, and where these mutations are located (see Figure 2). Given the well known, common structural characteristics of G protein-coupled receptors, one of ordinary skill in the art can easily extend these teachings to other G protein-coupled receptors without undue experimentation.

(3) State of the Prior Art

The Office Action at page 4 indicates that the "Mikayama and Voet references demonstrate that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function." Applicants note that the publication dates of the Voet and Mikayama references are 1990 and 1993, respectively. These dates are 8 and 5 years, respectively, before the July 28, 1998 priority date of the instant application.

Given the rapid changes in technology that occur in this particular field, the Voet and Mikayama references may not necessarily be considered state of the art at the time the instant application was filed. Indeed, although examples exist of polypeptide families wherein individual members have distinct, even opposite, biological activities, growing databases and improved search techniques, particularly the iterated PSI-BLAST tool, have yielded substantial improvement in secondary structure prediction accuracy. According to Rost, a copy of which is submitted herewith as Appendix B, "[s]econdary structure predictions are increasingly becoming the work horse for numerous methods aimed at predicting protein structure and function." Burkhard Rost, *Review: Protein Secondary Structure prediction Continues to Rise* (2001) J. Structural Biology 134: 204-218. Thus, Applicants respectfully submit that, although some references may critique the usefulness of approaches that predict protein function based on protein homology, the truth is that during the genomic era, prediction of protein function based

on protein homology was successfully achieved in a plethora of newly cloned molecules, including a plethora of newly cloned molecules that are the subject of multiple issued patents. In summary, it is irrelevant that some isolated references (such as the references cited by the Examiner) question the usefulness of the structure/function-based approach, because ***Applicants have successfully used this approach to predict the biological activity of the molecules of the present invention***.

(4) The Art is Highly Predictable

The Office Action indicates at page 4 that the "Mikayama and Voet references demonstrate the unpredictability of the protein art." In particular, the Office Action at page 3 states that "the unpredictability of the protein art is shown in Bowie *et al.* (*Science*, 1990, 247:1306 – 1310)," which teaches that "[c]ertain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (col. 2, page 1306)." The Office Action also indicates that the "sensitivity of proteins to alterations of even a single amino acid in a sequence are exemplified by Mikayama *et al.* (1993)." Furthermore, the Office Action indicates that "[i]t is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell," as exemplified in Voet *et al.* (1990), which teaches that a "single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph)" (see pages 3-4 of the Office Action). Applicants respectfully disagree.

It is Applicants' position that GPCRs were well known and extensively described in the art at the time the application was filed. Furthermore, the common physical characteristics and activities of GPCRs were well known to one of ordinary skill in the art at the time of filing. The instant specification is replete with structural and functional information on GPCRs (see, for example, pages 1-6, and Examples 1-3 of the specification, as well as Navarro *et al.* WO/92/18641 (1009, pages 14-15).

Also, as noted above, the publication dates of the Voet and Mikayama references are 1990 and 1993, respectively. These dates are 8 and 5 years, respectively, before the July 28, 1998 priority date of the instant application. Similarly, the Bowie *et al.* reference was published 8 years before the July 28, 1998 priority date of the instant application. Again, given the rapid changes in technology that occur in this particular field, the references cited by the Examiner may not necessarily constitute valid indicators of the unpredictability of the art. This is especially true in light of the ever growing databases and improved search techniques, particularly the iterated PSI-BLAST tool, that have yielded substantial improvement in secondary structure prediction accuracy. (See Rost, *Review: Protein Secondary Structure prediction Continues to Rise, supra.*)

(5) Level of Skill in The Art is High

Applicants note that the Office Action does not address "the level of skill in the art" as one of the Wands factors to be considered. Applicants assert that this factor is very important, and submit that the level of skill in the art is very high; at the level of a Ph.D. molecular biologist/biochemist. In summary, GPCRs have been thoroughly studied and the level of skill in the art is very high. The high level of skill in the art coupled with Applicants' teachings and the state of the art demonstrate that there is a high level of predictability in practicing the claimed invention.

(6) The Amount of Direction Provided by the Inventor

As noted above, Applicants have provided in the application more than ample direction to one of ordinary skill in the art to make and use the claimed invention without undue experimentation. Applicants teach a specific amino acid motif wherein one or more point mutations are introduced (see, for example, page 7, lines 17-34 of the specification). The resultant mutant receptors generate a greater signal than that generated by the corresponding wild-type receptors. Furthermore, Applicants disclose working examples that teach how to make and express GPCRs of the invention (see page 62, line 35 through page 67, line 48 of the specification). Given the well known, common structural characteristics of G protein-coupled receptors described above, one of ordinary skill in the art can easily extend these teachings to other G protein-coupled receptors without undue experimentation.

(7) The Existence of Working Examples

The Office Action indicates that Applicants have only provided working examples for a mutant IL-8A receptor and a mutant galanin receptor and no other mutant receptor proteins. Thus, it appears that the Examiner is in effect imposing an additional requirement, one not contained in 35 U.S.C. §112, of a working example or examples for each and every embodiment of the invention in order to enable the breadth of the claims.

Applicants assert that a working example is not required for enablement. See, *Shanks v. Scheffer*, 204 U.S.P.Q. 781, 783 (Pat. Bd. Inter. 1979). Moreover, "there is no magical relation between the number of representative examples and the breadth of the claims". *In re Borkowski and VanVenroy*, 164 U.S.P.Q. 642, 646 (C.C.P.A. 1970). Section 112 only requires that the "specification contain a written description of the invention, and the manner and process of making and using it". Applicants have fulfilled these requirements.

(8) The Quantity of Experimentation Needed to Make or Used The Invention

The Office Action at page 5 indicates that "a preponderance of the evidence demonstrates that it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention." This position is based by and large upon the Bowie, Voet and Mikayama references.

The key question then, is whether it would require undue experimentation to conduct Applicants' methods as broadly claimed. Enablement is not precluded by the necessity for some experimentation, and a considerable amount of experimentation is permitted. See, *In re Wands*, 8 U.S.P.Q. 2d 1400, 1404 (Fed. Cir. 1988). As discussed above, the Bowie, Voet and Mikayama references are not dispositive of the issue of unpredictability, especially in light of other references (*e.g.*, the Rost reference), the state of the art at the time the application was filed, the level of skill in the art, and the specific teachings and working examples provided by Applicants. Thus, the Bowie, Voet and Mikayama references do not provide the requisite "preponderance of the evidence". Based on the teachings of the specification as enumerated and cited above, and still further based on the specification's working examples, ***which the Examiner clearly admits enable practice of the claimed method with the disclosed species***, Applicants submit that one

skilled in the art would be able to make and use the claimed methods without undue experimentation.

Based on the foregoing, Applicants respectfully request that the section 112, first paragraph rejection be withdrawn.

Rejection of Claims 1-14, and 43-59 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected Claims 1-14 and 43-59 under 35 U.S.C. §112, first paragraph "as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was field, had possession of the claimed invention." In particular, the Office Action asserts that

> [t]he written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show that application was in possession of the claimed genus.

Applicants respectfully traverse the aforementioned rejection for at least the following reasons. Applicants respectfully submit that there is sufficient written description in Applicants' specification regarding the claimed molecules, to inform a skilled artisan that Applicants were in possession of the claimed invention at the time the application was filed, as required by section 112, first paragraph (see M.P.E.P. §2163.02). "Written description may be satisfied through disclosure of relevant identifying characteristics, *i.e.*, structure, other physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. §112, First Paragraph Written Description Requirement.* Moreover, "[a] specification may, within the meaning of 35 U.S.C., §112, First Paragraph, contain a written description of a broadly written claimed invention without describing all species that claim encompasses." *Utter v. Hiraga*, 845 F.2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988). Moreover, the *In re Grimme* case sets out the following language with respect to the written description requirement, "[i]t may not be necessary to

enumerate a plurality of species if a genus is sufficiently identified in an application by 'other appropriate language.'" *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960).

For reasons discussed in detail below, the instant specification satisfies this requirement for the claimed invention. It is Applicants' position that the claimed genus of the mutant GPCRs of the present invention is defined by structural features that are described in the specification, recited in the claims, and commonly possessed by its members. In particular, the structure of the claimed genus is taught in the specification, *i.e.*, the structure of the mutant GPCR, the corresponding the amino acid motif [$X_1X_2X_3X_4$] and the position of the point mutation within the amino acid motifs (see page 7, line 17 through page 8, line 40 of the specification). Furthermore, this structure was already well-know in the art through such publications as, for example, Navarro *et al.* WO/92/18641.

Contrary to the Examiner's assertion, Applicants respectfully submit that the instant specification teaches distinguishing structural features within the claimed genus. For example, the instant specification discloses the amino acid sequence of the rabbit IL8A receptor showing putative membrane spanning domains, *e.g.*, Arg73 (1st intracellular loop), Met246 (3rd intracellular loop) and Gly320 (C-terminal tail) (see page 10, lines 19-21 of the specification. Moreover, G-protein coupled receptors are known molecules with a conserved structure.

In summary, Applicants have described a genus of mutant GPCRs based on structural features that are common to a substantial portion of the genus and have provided within the instant specification the amino acid motifs and the point mutations within the amino acid motif that possess these features. Accordingly, Applicants submit that the present invention satisfies the requirements of 35 U.S.C. §112, first paragraph.

Rejection of Claims 1, 8, and 13 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected Claims 1, 8, and 13 under 35 U.S.C. §112, second paragraph because "the term 'proximal' is a relative term which render the claim indefinite."

Applicants respectfully traverse the foregoing rejection and submit that because the Applicant did not provide a definition of the term "proximal" in the specification, the claim language should be given its plain meaning. *See In re Zletz*, 893 F.2d 319, 321, 13 USPQ2d 1320, 1322 (Fed. Cir. 1988). Thus, according to Webster's Dictionary (Deluxe Edition, 1998, submitted herewith as Appendix C), the word "proximal" is defined as: situated close to.

Applicants respectfully submit that based on this plain meaning, in combination with the specific examples given in the specification, one of ordinary skill in the art would know that the term "proximal," in the context of Claim 1 and the claims depending therefrom, indicates the position of the amino acid motif relative to the N-terminal and C-terminal ends; i.e., the amino acid motif is closer to the C-terminus than it is to the N-terminus. Indeed, the Examiner had no trouble construing this term, inasmuch as the Examiner has cited, for example, the Navarro *et al.* published PCT as allegedly teaching an LFGA motif "***near*** the carboxy terminal", the Bergsman *et al.* published PCT as allegedly teaching a "PPLA motif ***proximal*** to the carboxy terminal", and the Hinuma et al. published European patent application as allegedly teaching an FLSE motif "***near*** the carboxy terminal". (see Office Action at page 8, first paragraph, page 9, second paragraph, and page 10, second paragraph, respectively).

Thus, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims Under 35 U.S.C. § 102

Rejection of Claims 1, 5, 8, and 10-11 Under 35 U.S.C. §102

The rejection of Claims 1, 5, 8, and 10-11 has been maintained under 35 U.S.C. §102 (b), "as being anticipated by Navarro *et al.* (WO 92/18641)." In particular, the Office Action, at page 8, states that

> Navarro *et al.* discloses a mammalian IL8 receptor (page 10, lines 5-14). This receptor comprises a LFGA motif near the carboxy terminal (Figure 1, drawing Sheet 2, third line; Sequence Comparison A), and a seventh transmembrane domain.

Applicants respectfully traverse the foregoing rejection of Claim 1, and the claims depending therefrom, for the reasons of record set forth in Applicants' Amendment and Response submitted to the United States Patent and Trademark Office on December 5, 2000. Applicants reassert the substance of those arguments herein.

For a reference to anticipate a claimed invention under 35 U.S.C. §102, the reference must teach ***each and every element*** of the claimed invention. See M.P.E.P. 2143. Claim 1 is directed to a mutant mammalian G-protein coupled receptor having an amino acid sequence which differs from a wild type G protein-coupled receptor having a wild type amino acid

sequence comprising the amino acid motif ($X_1X_2X_3X_4$) proximal to the carboxy terminal end of said wild type amino acid sequence, ***which contains at least one point mutation at a position in said amino acid motif; such that upon interaction with a ligand***, said mutant receptor is capable of modulating a signal transduction pathway in a cell, ***wherein a signal generated by said mutant receptor is greater than a signal generated upon interaction of said ligand with a wild type G protein-coupled receptor***.

Navarro *et al.* teach an amino acid sequence (SEQ ID NO:1) of a receptor that is identical to the wild-type rabbit sequence (see Pub Med Accession # P21109). Although Navarro *et al.* indicate in passing that specific analog receptors of interest include full-length or partial receptor proteins including an amino acid sequence which differs only by conservative amino acid substitutions, for example, substitution of one amino acid or another of the same class, or by one of more non-conservative amino acid substitutions, deletions or insertions, there is no teaching or suggestion of such conservative or non-conservative amino acid substitutions deletions, or insertions specifically in the wild-type LFGA motif near the carboxy terminal. Therefore, contrary to the assertion in the last paragraph on page 8 of the Office Action, the sequence disclosed by Navarro *et al.* does not have the identical structure with the mutant motif of the instant invention. In fact, there doesn't appear to be any disclosure in the reference of any mutated sequences, much less IL-8 receptor protein sequence with a mutation in the motif cited by the Examiner.

Moreover, there is no teaching or suggestion in the reference that a receptor protein containing such a mutated motif would cause a greater degree of signaling as compared to the wild-type receptor protein. As indicated in the Office Action, a chemical composition and its properties are inseparable. However, the chemical composition disclosed by Navarro *et al.* does not possess the property of increased signaling because it does not have the necessary structure, *i.e.*, a mutation in the amino acid motif, necessary to bring about that property.

Because (1) SEQ ID NO:1 is not a mutant of the wild type sequence; (2) the Navarro *et al.* reference gives no specific disclosure of a mutation within the $X_1X_2X_3X_4$ motif; and (3) Navarro *et al.* neither teach nor suggest a substitution in this sequence that would cause a signal to be generated upon ligand binding that is greater than a signal generated by the wild-type receptor, Applicants respectfully submit that Navarro *et al.* fail to teach ***each and every element***

of Claim 1 and the claims depending therefrom. In view of the foregoing, Applicants respectfully request that this section 102(b) rejection be reconsidered and withdrawn.

Rejection of Claims 1-2, 4-5, and 11-12 under 35 U.S.C. §102 (b)

The rejection of Claims 1-2, 4-5, and 11-12 has been maintained under 35 U.S.C. §102 (b), "as being anticipated by Bergsman *et al.* (WO 96/18651)." In particular, the Office Action, at page 9, states that

> Bergsman *et al.* discloses a human somatostatin receptor (page 3, line 23). The receptor comprises a PPLA motif proximal to the carboxy terminal (page21, third line; Sequence Comparison B), and a seventh transmembrane domain. Bergsman *et al.* discloses that mutants of the receptor may be prepared by the deletion of a portion of the sequence encoding the protein, by insertion of a sequence, and/or by substitution of one or more nucleotides within the sequence.

Applicants respectfully traverse the foregoing rejection of Claim 1 and the claims depending therefrom for the reasons of record in the Response and Amendment filed with the United States Patent and Trademark Office on December 5, 2000. However, Applicants maintain that the rejection should be withdrawal and therefore reassert herein the substance of the arguments earlier presented.

For a reference to anticipate a claimed invention under 35 U.S.C. §102, the reference must teach ***each and every element*** of the claimed invention. See M.P.E.P. 2143. Claim 1 is directed to a mutant mammalian G-protein coupled receptor having an amino acid sequence which differs from a wild type G protein-coupled receptor having a wild type amino acid sequence comprising the amino acid motif ($X_1X_2X_3X_4$) proximal to the carboxy terminal end of said wild type amino acid sequence, ***which contains at least one point mutation at a position in said amino acid motif***; such that upon interaction with a ligand, said mutant receptor is capable of modulating a signal transduction pathway in a cell, ***wherein a signal generated by said mutant receptor is greater than a signal generated upon interaction of said ligand with a wild type G protein-coupled receptor.***

Bergsman *et al.* teach an isolated human somatostatin-like receptor (SEQ ID NO:2) containing the wild-type sequence of the receptor (see Pub Med Accession # AAC14587).

Although Bergsman *et al.* indicate in passing that it may be desirable to produce mutants of the receptors of interest by deletion of a portion of the sequence encoding the protein, by insertion of a sequence, and/or by substitution of one or more nucleotides within the sequence, there is no teaching or suggestion of producing a mutation into wild-type PPLA motif proximal to the carboxy terminal. Therefore, contrary to the assertion in the last paragraph on page 9 of the Office Action, the sequence disclosed by Bergsman *et al.* does not have the identical structure with the mutant motif of the instant invention. In fact, there doesn't appear to be any disclosure in the reference of any actual mutated sequences, much less a human somatostatin-like receptor protein sequence with a mutation in the motif cited by the Examiner.

Moreover, there is no teaching or suggestion in the reference that a receptor protein containing such a mutated motif would cause a greater degree of signaling as compared to the wild-type receptor protein. As indicated in the Office Action, a chemical composition and its properties are inseparable. However, the chemical composition disclosed by Bergsman *et al.* does not possess the property of increased signaling because it does not have the necessary structure, *i.e.*, a mutation in the amino acid motif, necessary to bring about that property.

Because (1) SEQ ID NO:2 is not a mutant of the wild type sequence; (2) the Bergsman *et al.* reference gives no specific disclosure of a mutation within the $X_1X_2X_3X_4$ motif; and (3) Bergsman *et al.* neither teach nor suggest a substitution in this sequence that would cause a signal to be generated upon ligand binding that is greater than a signal generated by the wild-type receptor, Applicants respectfully submit that Bergsman *et al.* fail to teach each and every element of Claim 1 and the claims depending therefrom. In view of the foregoing, Applicants respectfully request that this section 102(b) rejection be reconsidered and withdrawn.

Rejection of Claims 1, 5, and 11-13 under 35 U.S.C. §102 (b)

The rejection of Claims 1, 5, and 11-13 have been maintained under 35 U.S.C. §102 (b), "as being anticipated by Hinuma *et al.* (EP 0711830A2)." In particular, the Office Action, at pages 9 and 10, states that

> Hinuma *et al.* discloses a human galanin receptor (page 4, line 58 to page 5, line 8). The receptor comprises an FLSE motif near the carboxy terminal (page 58, amino acids 305-309), and a seventh transmembrane domain. Hinuma *et al.* discloses that the galanin

> receptor protein can be modified by, *e.g.*, addition, deletion, substitution with other amino acids, etc (page 15, lines 49-50).

Applicants respectfully traverse the foregoing rejection of Claim 1 and the claims depending therefrom for the reasons of record in the Response and Amendment filed with the United States Patent and Trademark Office on December 5, 2000. However, Applicants maintain that the rejection should be withdrawal and therefore reassert herein the substance of the arguments earlier made of record.

For a reference to anticipate a claimed invention under 35 U.S.C. §102, the reference must teach ***each and every element*** of the claimed invention. See M.P.E.P. 2143. Claim 1 is directed to a mutant mammalian G-protein coupled receptor having an amino acid sequence which differs from a wild type G protein-coupled receptor having a wild type amino acid sequence comprising the amino acid motif ($X_1X_2X_3X_4$) proximal to the carboxy terminal end of said wild type amino acid sequence, ***which contains at least one point mutation at a position in said amino acid motif***; such that upon interaction with a ligand, said mutant receptor is capable of modulating a signal transduction pathway in a cell, ***wherein a signal generated by said mutant receptor is greater than a signal generated upon interaction of said ligand with a wild type G protein-coupled receptor***.

Hinuma *et al.* teach an isolated human galanin receptor (Figure 6) containing the wild-type sequence of the receptor (see Pub Med Accession # P25024). Although Hinuma *et al.* indicate in passing that a portion of the amino acid sequence may be modified by, *e.g.*, addition, deletion, substitution with other amino acids, *etc.* in the galanin receptor proteins, there is no teaching or suggestion of producing a mutation into wild-type FLSE motif near the carboxy terminal. Therefore, contrary to the assertion in the last paragraph on page 10 of the Office Action, the sequence disclosed by Hinuma *et al.* does not have the identical structure with the mutant motif of the instant invention. In fact, there doesn't appear to be any disclosure in the reference of any actual mutated sequences, much less a galanin receptor protein sequence with a mutation in the motif cited by the Examiner.

Moreover, there is no teaching or suggestion in the reference that a receptor protein containing such a mutated motif would cause a greater degree of signaling as compared to the wild-type receptor protein. As indicated in the Office Action, a chemical composition and its properties are inseparable. However, the chemical composition disclosed by Hinuma *et al.* does

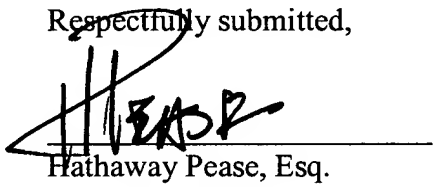
not possess the property of increased signaling because it does not have the necessary structure, *i.e.*, a mutation in the amino acid motif, necessary to bring about that property.

Because (1) the isolated human galanin receptor is not a mutant of the wild type sequence; (2) the Hinuma *et al.* reference gives no specific disclosure of a mutation within the $X_1X_2X_3X_4$ motif; and (3) Hinuma *et al.* neither teach nor suggest a substitution in this sequence that would cause a signal to be generated upon ligand binding that is greater than a signal generated by the wild-type receptor, Applicants respectfully submit that Hinuma *et al.* fail to teach each and every element of Claim 1 and claims depending therefrom. Based on the foregoing, Applicants respectfully request that this section 102(b) rejection be reconsidered and withdrawn.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



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